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Review Article

Hypertrophic cardiomyopathy—What is new?

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ABSTRACT

This work covers new findings on hypertrophic cardiomyopathy. The definition, genetic findings, genotype-phenotype relationships, incidence, and prognosis of the disease are reviewed. The latest recommendations for treatment are discussed, particularly percutaneous transluminal septal myocardial ablation and septal myectomy in severely symptomatic obstructive forms.

Contents

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1. Introduction

Hypertrophic cardiomyopathy (HCM) is a disease characterized by hypertrophy of the interventricular septum and/or left ventricle, diastolic dysfunction, and in some patients also by systolic obstruction in the left and rarely right outflow tract [1,2]. The disease was described for the first time in 1957 by Brock (quotation from 1). The detailed pathological-anatomical description was published by Teare next year (quotation from 1). He likened the marked myocardial hypertrophy to a tumor of the heart.

The view on HCM has changed many times since that time. The aim of our work is to summarize knowledge, which has changed our view on various aspects of HCM in last years.

2. What is considered HCM?

The publication of the new classification of European Society of Cardiology that significantly changed definition of HCM meant the first substantial change [3]. According to the new classification, cardiomyopathies are disorders in which cardiac muscle is structurally and functionally abnormal in the absence of another cardiac disease, including CAD, hypertension, valve disease, or congenital heart disease that would cause myocardial abnormality. It means that while only idiopathic forms were considered HCM until recently, now also other conditions that may cause hypertrophy are ranked among HCMs, for example lysosomal storage disorders (Fabry's disease), glycogen storage diseases (Pompe's disease, Danon's disease), myocardial hypertrophy in Friedreich's ataxia, or initial stages of amyloidosis, Noonan's syndrome, mitochondrial diseases, carnitine deficiency, or hypertrophy in infants of diabetic mothers, etc. In our text, we will focus on "classic" so called idiopathic forms of HCM since covering the whole spectrum of cardiomyopathies is beyond the scope of this paper.

3. Etiology of HCM—genetics

Since the beginning, HCM unlike dilated cardiomyopathies was known to be a genetic disorder. It was assumed that detailed genetic testing in this disease will bring important findings. HCM is also the first cardiologic disorder studied at the molecular level and is used as a model for genetic studies. Mutations of genes encoding the cardiac sarcomere are responsible for pathogenesis of this disease. The first important information on this topic was published in 1989 when Jarcho et al. proved association between HCM and a locus mapped to the long arm of chromosome 14 [4]. They presumed that the candidate gene responsible for HCM was one of the genes for beta-myosin or heat shock protein. Its precise identification was not long awaited. One year later, Salomon et al. discovered that the gene for beta-myosin is responsible for familiar HCM [5]. This finding raised big expectations because the identification of the candidate gene could have led to precise mapping of responsible mutation by PCR or direct sequencing. Thereafter nothing would be in the way of application of genetic methods in direct diagnostics, genetic counseling, and eventually also in prenatal diagnostics [6].

The situation became complicated when it had proved that at least in two families with HCM, the gene responsible for the disease had not been located on the chromosome 14 [5]. The hypothesis was proposed that HCM could have been caused by mutations in two different genes that encoded different proteins with similar function. Since we know that the beta-myosin is a protein of the muscle sarcomere, further attention was concentrated on its other components. Other genes (or rather their products—proteins) responsible for HCM have also been identified one by one. They are listed in Table 1.

At present, more than 1000 mutations in above mentioned genes are known. However, none of the mutations is predominant [7]. The most mutations have been found in the gene for the beta-myosin heavy chain and myosin binding protein C. Surprisingly in the Czech population, mutations in the gene for the myosin binding protein C are more common than for beta-myosin heavy chain. New unknown mutations are still being discovered [8,9]. The mutation distribution along genes is uneven. There are regions with their frequent occurrence and, on the contrary, regions where no mutation has been found [10].

The former concept that the certain genotype is associated with the specific form of HCM with particular morphological and functional features and prognosis has not been confirmed [8]. For example, it was reported in the past that the mutation in the cardiac troponin T gene was associated with

Table 1 – Genes responsible for HCM.

Protein and gene abbreviation	Locus	Component of the sarcomere	Frequency (%)
Beta-myosin heavy chain (MYH7)	14q12	Thick filaments	44
Myosin binding protein C (MYPBC3)	11p11.2	Thick filaments	35
Troponin T (TNNT2)	1q32	Thin filaments	7
Troponin I (TNNI3)	19p13.4	Thin filaments	5
Alpha-tropomyosin (TPM1)	15q22.1	Thin filaments	2.5
Cardiac myosin light chain, regulatory (MYL2)	12q24.3	Thick filaments	2
Cardiac myosin light chain, essential (MYL3)	3p21	Thick filaments	1
Aktin (ACTC)	15q14	Thin filaments	1
Titin (TTN)	2q31	Thick filaments	<1
Cardiac LIM protein (CSRP3)	11p15.1	Z-disc	<1
Telethonin (TCAP)	2q24.3	Z-disc	<1
Myozenin 2 (MYOZ2)	7q36	Z-disc	<1
Vinculin (VCL)	14q11.2	Intercalated disc	<1

mild (or even none) hypertrophy but serious prognosis of sudden death [11], however, it has been found later that this risk might be, on the contrary, very low [12].

4. Is HCM a rare disease?

The answer to this question has changed significantly in last years. Epidemiological studies in various populations have shown consistent prevalence rates of phenotypic features of HCM in adult population of approximately 0.2% (1 out of 500 adults) [13,14]. Low occurrence of this condition among common cardiological patients – around 1% of patients referred for an echocardiographic examination [13] – can be explained by the fact that majority of the patients are asymptomatic and that is why they escape diagnosis. The prevalence rate of HCM ranges from 0.02 to 0.2%. Nowadays, rather the upper limit of this range 0.2% is widely accepted. It accounts for about 20,000 patients in Czech Republic [2], and we still discuss only so-called idiopathic forms and do not include conditions falling under the extended definition of cardiomyopathies by ESC. Therefore we do not refer to HCM as a rare disease, but as the most common monogenic genetic disorder.

The primary screening method is ECG, which is pathological in 75% to 95% of patients. The ECG changes may precede development of hypertrophy and/or clinical symptoms [15]. The gold standard for the diagnosis of HCM is echocardiography. An echocardiogram shows idiopathic left ventricular hypertrophy (in most cases more than 15 mm in men and 13 mm in women) [16].

5. Obstruction

We do not deal with obstruction in details in this paper, two newer findings should be, however, mentioned in this context. Mitral valve leaflets elongation have been proven in HCM. This morphological abnormality is responsible for left ventricular obstruction in combination with small outflow tract dimension [17].

Isosorbide dinitrate appeares reliable provoking test for detection of HCM obstruction with good sensitivity and specificity [18]. Measurement should be delayed 5–10 min after application of ISDN.

6. What is prognosis of HCM?

Until recently, it was generally accepted that HCM was a disease with utterly unfavorable prognosis. It was believed that those affected were anytime in danger of sudden death, which struck more likely majority of them. The mortality rate was estimated at 2% to 4% in adults and 6% in children. The majority of deaths were sudden [19,20].

Current opinions on this issue are completely different. HCM is a relatively benign disease with the annual mortality rate falling below 1% in last 40 years. Approximately one half of deaths are sudden and the rest of them are caused by heart failure and stroke [21,22]. The situation has not changed as a consequence of better treatment (with an exception of ICD implantation in last years), but rather due to more sensitive diagnostic procedures. We are able to recognize milder forms of the disease, which was not possible to identify before. Particularly asymptomatic and oligosymptomatic patients have a favorable prognosis, while patients with severe left ventricular outflow tract obstruction (Vmax > 4 m/s) have worse prospects, and course of the disease is more frequently complicated by heart failure in those patients [23].

However, it would be wrong to be excessively optimistic. HCM still takes its toll in deaths, especially of young people. For example, in children 6 to 18 years of age, HCM is the main cause of sudden death, together with arrhythmogenic right ventricular dysplasia [24].

7. How to treat HCM?

Most of the symptoms in non-obstructive forms of HCM are caused by diastolic dysfunction [25]. Since treatment of diastolic dysfunction is problematic, also treatment of non-obstructive HCM is difficult. Beta-blockers or calcium channel blockers (verapamil, diltiazem) are commonly used.

Also therapy with ACE inhibitors has some therapeutic potential, as we already demonstrated 15 years ago [26]. Since we were not able to arrange a double-blind, placebo-controlled trial at that time for financial reasons, our results had only limited validity. Further data confirmed later that it was useful to study drugs acting on renin–angiotensin–aldosterone system in patients with HCM [27]. Later we managed to organize a double-blind, placebo-controlled trial with candesartan and its results were very encouraging [28–30].

A very important treatment modality is ICD implantation. ICD should be implanted in patients with HCM who have at least one of five known risk factors of sudden cardiac death (family history of sudden cardiac death, syncope, LV wall thickness more than 30 mm, abnormal exercise blood pressure, nonsustained ventricular tachycardia), or personal history of spontaneous sustained ventricular tachycardia, or cardiac arrest [31]. CMR late gadolinium enhancement defined fibrosis had been linked to the substrate for VT/VF and it may probable serve as a predictor of thise arrhythmias in HCM patients [32]. As far as ICD implantation is concern, there may be a higher risk for device complications and inappropriate shocks in HCM, especially of younger patients and those with atrial fibrillation [33].

There are several other options of treatment for patients with obstructive HCM. Disopyramide – a type I antiarrhythmic drug with negative inotropic action – can be administered. However, this drug is not used in Czech Republic. We can also recommend beta-blockers and calcium channel blockers in this indication. Though calcium channel blockers might be associated with obstruction worsening (probably due to vasodilatation) and increased incidence of sudden death in patients with severe obstruction [19,25].

Dual chamber pacing has been used historically in patients with obstructive HCM. This treatment option has proven to be less effective than expected and it acts as placebo in many cases [34]. Nowadays, dual chamber pacing is recommended in those symptomatic patients in whom myectomy or

percutaneous transluminal septal myocardial ablation (PTSMA) cannot be performed [35].

8. Is better PTSMA or surgical myectomy?

Both methods play an essential role in symptomatic patients with obstructive form. It has been repeatedly discussed recently which of the above mentioned methods is better and more beneficial for patients. Unfortunately, no randomized trial has been performed that would resolve this question and according to some authors, it is not feasible to design such trial [36]. Therefore it is not possible to get a conclusive answer, but we still can try to answer this question. Cardiac surgery – transaortic septal myectomy – was introduced already almost half a century ago by Morrow (also called Morrow procedure). Septal myectomy still remains gold-standard therapy in the USA. The surgery has now low mortality (below 0.5% in experienced centers) and might be associated with lower incidence of sudden cardiac death in comparison to remaining HCM population [37–39]. Mitral regurgitation improves in most cases after procedure or it can be specifically treated during surgery in severe cases (for example mitral valve repair can be performed if prolapse is present).

During PTSMA, concentrated alcohol is injected into the first and in some case also second septal branch of the left anterior descending artery. Shorter hospital stay and absence of sternotomy are advantages of PTSMA. A drawback of this procedure may be necessity of pacemaker placement in some patients (20–25% formerly, now in experienced centers around 10%) [37,40]. Procedural success is achieved in 70–75% of cases. The resultant myocardial infarctions after PTSMA are small, but they still could create new arrhythmogenic substrates. Nevertheless higher incidence of arrhythmogenic complications has not been proved so far. The mortality rate of this procedure is now 1–2% [41,42]. Lately, PTSMA is predominant in Europe, even in countries as Germany where transaortic septal myectomies were more common in the past.

Symptomatic improvements are comparable after both procedures. However, improvement after myectomy appears to be more durable and slightly more prominent, even in exercise parameters [43,44]. Also further prospect of patients is probably better after the surgical procedure [33,40]. American guidelines recommend choosing surgical myectomy in symptomatic, particularly younger individuals, while PTSMA mostly in those cases where operation is contraindicated, particularly in older patients [45]. Meta-analyses comparing both methods do not show consistent results. Two publications have not reported differences in incidence of sudden cardiac death and overall mortality [43,46]. Results of other works however have suggested bigger benefit after septal myectomy, both in lower mortality rates (early and late mortality) and symptomatic improvement of patients [42,47,48]. On top of that, the effect of the operation appears to be more stable [49]. Also other factors play an important role and they can influence outcome of PTSMA—for example the amount of injected ethanol [40,50], and generally also presence and nature of comorbidities [51]. Experience of the center with the particular method is important too. This experience is given mostly by number of performed procedures, which can create a limitation in Czech Republic.

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